Radiation Dose Calculations in Persons Receiving Injection of Samarium-153 EDTMP

K.W. Logan, W.A. Volkert, and R.A. Holmes

Department of Radiology and Section of Nuclear Medicine, University of Missouri-Columbia and Harry S. Truman Memorial Veterans Hospital, Columbia, Missouri

Samarium-153 EDTMP has been proposed as a radionuclide therapeutic agent to treat malignant bone tissue disorders. Data obtained from laboratory rats has been used to calculate the radiation dose for humans following the administration of [^{153}Sm]EDTMP. The data reveals that the highest doses are present in the skeleton and the urinary bladder wall (bladder dose varies with frequency of voiding). Skeletal activity was used to estimate the bone marrow dose from the [^{153}Sm]EDTMP beta radiation. Although this estimate indicates high marrow irradiation it is only an approximation since the beta radiation from inhomogeneously deposited bone activity surrounding the marrow produces variable radiation dose distributions.

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The dosimetry calculations for samarium-153 ethylenediaminetetramethylenephosphonic acid ([^{153}Sm]EDTMP) can be divided into two sections using formulations developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (*1*). The first involves the biologic distribution of the radiotracer in experimental animals. Time dependent activity concentrations in various organs and organ systems are converted to the MIRD "cumulated activity" or "A-tilde" ($\tilde{A}$) quantities, which gives the net number of disintegrations in each source organ in the biologic system.

The second section is the calculation of terms (absorbed dose per unit cumulated activity or "S" factors) describing the radiation dose (rad) in various target organs as a function of the cumulated activity distribution. Input to calculate the "S" factor includes the emission properties of ^{153}Sm and the absorption and attenuation characteristics of its emissions in a model of the adult body developed by the MIRD committee (*2*). The cumulated activity and "S" factor arrays are combined to give the calculated total radiation dose per injected mCi of [^{153}Sm]EDTMP to 14 target organs and organ systems.

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For reprints contact: K.W. Logan, Dept. of Radiology and Section of Nuclear Medicine, University of Missouri-Columbia and Harry S. Truman Memorial Veterans Hospital, One Hospital Dr., Columbia, MO 65212.

METHODS AND RESULTS

Cumulated Activity

Biodistribution. The estimated distribution of [^{153}Sm]-EDTMP in the human body is derived from experimental biodistributions of activity in rats as a function of time post-injection [pi] (*3*). A summary of animal distribution data is given in Table 1. To assume that the distribution of i.v. [^{153}Sm]EDTMP in humans is identical to rats is incorrect, however, the data does provide a reasonable estimate when human biodistribution results are not available. Several assumptions were made to logically represent the fractional distribution of this agent in the human body. Specifically, the dose to the bladder depends on the voiding frequency and the volume of urine excreted into the urinary tract during the first 24 hr after the injection. Conservatively, we assumed that during the initial 5 hr 75% of the urine was voided and that the remaining 25% was excreted to zero bladder activity at 24 hr. An average bladder content of 200 g was used to calculate the dosimetry values. Hydration with more rapid voiding could lower bladder activity and radiation levels, while poorer hydration might slow the voiding process and increase the bladder radiation dose.

The fraction of administered activity concentrating in skeletal bone was estimated from femur activity measured in the rat experiments. The assumption was made that total-body skeleton concentration (fraction of administered activity) was

25 times the measured femur activity. All of the organ activity concentrations, except bone and bladder urine accumulating beyond 24 hr, were considered constant based on the average values measured at 24, 48, and 72 hr. The concentrations measured at these later times were constant within 1 s.d.

To generate human dose values for the upper and lower large intestine, since the animal data did not differentiate these structures, a final assumption was made. The percent of administered tracer measured in the total large intestine from the animal data was assumed to be distributed according to the volume (mass) content of the upper and lower large intestine for the human calculations. The mass of the two contents used for this distribution was the values given in the MIRD model (*5*).

Cumulated Activity Calculations

The cumulated activity in an organ is defined as the integral of the activity present over the time interval for which the dose is to be calculated in units of mCi-hr. The time interval for most radiopharmaceuticals extends from the time of injection to infinity. This was calculated numerically for the ten source organs listed in Table 2, using the fraction of administered [^{153}Sm]EDTMP measured in the animal tissues at different times p.i. and the biodistribution assumptions given above. The concentrations (% of administered activity) present in the various organs at 0.25, 0.5, 1, 2, 5 and 24 hr p.i. were used in the calculations. The cumulated activity for each organ was obtained by stepwise integration between each time point. The cumulated activity integration assumes that [^{153}Sm]EDTMP organ concentration is represented by the arithmetic mean of the levels at the beginning and end of each interval. The general form of integration for each source organ is:

$$\tilde{A} = \frac{A_{(0.25)}}{2}\int_0^{0.25h} e^{-\lambda t}\,dt + \frac{A_{(0.5)}+A_{(0.25)}}{2}\int_{0.25h}^{0.5h} e^{-\lambda t}\,dt + \frac{A_{(0.5)}+A_{(1)}}{2}\int_{0.5h}^{1h} e^{-\lambda t}\,dt + \frac{A_{(1)}+A_{(2)}}{2}\int_{1h}^{2h} e^{-\lambda t}\,dt + \frac{A_{(2)}+A_{(5)}}{2}\int_{2h}^{5h} e^{-\lambda t}\,dt + \frac{A_{(5)}+A_{(24)}}{2}\int_{5h}^{24h} e^{-\lambda t}\,dt + \frac{A_{(24)}+A_{(t+)}}{2}\int_{24}^{\infty} e^{-\lambda t}\,dt \quad (1A)$$

$$\tilde{A} = \frac{1}{\lambda}\left[\frac{A_{(0.25)}}{2}(1-e^{-0.25\lambda}) + \frac{A_{(0.5)}+A_{(0.25)}}{2}(e^{-0.25\lambda}-e^{-0.5\lambda}) + \frac{A_{(1)}+A_{(0.5)}}{2}(e^{0.5\lambda}-e^{-\lambda}) + \frac{A_{(2)}+A_{(1)}}{2}(e^{-\lambda}-e^{-2\lambda}) + \frac{A_{(5)}+A_{(2)}}{2}(e^{-2\lambda}-e^{-5\lambda}) + \frac{A_{(24)}+A_{(5)}}{2}(e^{-5\lambda}-e^{-24\lambda}) + \frac{A_{(24)}+A_{(t+)}}{2}e^{-24\lambda}\right]. \quad (1B)$$

The constants A(0.25), A(0.5), A(1), A(2), A(5), and A(24) are the percent of injected dose in the organ at 0.25, 0.5, 1, 2, 5, and 24 hr. A(t+) is the percent of injected dose in the organ beyond 24 hr, and as shown above, A(t+) is assumed to be constant. The value of λ is 0.01484/hr. For all source organs except bone, Eq. (1B) becomes:

$$\tilde{A} = 67.385\left[\frac{A_{(0.25)}}{2}\times 3.7038\times 10^{-3} + \frac{A_{(0.5)}+A_{(0.25)}}{2}\times 3.69\times 10^{-3} + \frac{A_{(1)}+A_{(0.5)}}{2}\times 7.34\times 10^{-3} + \frac{A_{(2)}+A_{(1)}}{2}\times 1.45\times 10^{-2} + \frac{A_{(5)}+A_{(2)}}{2}\times 4.228\times 10^{-2} + \frac{A_{(1)}+A_{(5)}}{2}\times .228 + \frac{A_{(24)}+A_{(t+)}}{2}\times 0.7003\right]. \quad (2)$$

For bone, since the concentration of ^{153}Sm is constant beyond 5 hr, Eq. (2) becomes:

$$\tilde{A} = 67.385\left[\frac{A_{(25)}}{2}\times 3.7038\times 10^{-3} + \frac{A_{(0.5)}+A_{(0.25)}}{2}\times 3.69\times 10^{-3} + \frac{A_{(1)}+A_{(0.5)}}{2}\times 7.34\times 10^{-3} + \frac{A_{(2)}+A_{(1)}}{2}\times 1.451\times 10^{-2} + \frac{A_{(5)}+A_{(2)}}{2}\times 4.228\times 10^{-2} + A_{(+5h)}\times 0.92847\right]. \quad (3)$$

The cumulated activities for ten source organs were calculated using the data in Table 1, the biodistribution assumptions above, and Eqs. (2) and (3). The results are listed in Table 2.

"S" Factor Calculations for ^{153}Sm

Because ^{153}Sm has not been used medically or has previously been present as a radionuclide contaminant no set of ^{153}Sm "S" factors employing the MIRD dosimetry technique has been included in the MIRD publications. The "S" factor for target organ j and source organ k is given by:

$$S(j, k) = \sum_i \Delta_i \Phi_{ijk}. \quad (4)$$

The Δ_i terms are the mean energy emitted per unit cumulated activity for the various i-type radiations (i-type emissions), and are taken from Appendix A.3 of Reference *4*.

The Φ_{ijk} terms in Eq. (4) are the specific absorbed fractions that depend on the properties of the i-type emission and the size, shape, and separation of the source and target organs. Specific absorbed fractions are not available in the literature for many individual radionuclides (including ^{153}Sm). To address this, the MIRD committee has published a "generalized" means to calculate specific absorbed fractions from the results of Monte Carlo calculations of photon transport in the adult human body using a mathematical phantom (*2*). These calculations are tabulated as specific absorbed fractions at various discrete photon energies for a number of source and target organs. The significant photon emissions for ^{153}Sm (*4*) are listed in Table 3. To calculate the ^{153}Sm "S" factors, the energy content (Δ_i) of the three K shell x-rays were summed, and included in the calculations as single Φ_{ijk} value at 40 keV. Photons emitted with <1% intensity were omitted, and the L shell x-ray at 6 keV was assumed to be absorbed like an

TABLE 1
Biodistribution of [^{153}Sm]EDTMP with Time in Rats (0 s.d. 190–210 g N = 5)

	Percent administered activity						
	15 min	30 min	1 hr	2 hr	5 hr	24 hr	T+
Blood	5.85	2.30	0.532	.0	0.007	0.007	0.006
Liver	0.96	0.52	0.322	0.25	0.37	0.35	0.43
Stomach	0.39	0.99	0.166	0.24	.06	.04	0.054
Large intestine	0.61	0.26	0.089	0.09	1.18	.05	0.06
Small intestine	0.79	0.50	0.342	0.75	0.33	0.04	0.053
Kidneys	1.74	0.80	0.46	0.25	0.36	0.25	0.25
Muscle	8.85	4.57	1.66	0.22	0.06	0.12	0.11
Femur	1.90	2.12	2.30	2.30	2.34	2.34	2.34
Urine	28.37	42.15	46.87	49.11	46.08/ 11.52†	0.00	0.00
Skeleton*	47.56	52.95	57.549	57.710	58.535	56.93	56.93

* Based on % dose femur × 25.
† Assumption of 75% voiding at 5 hr. Continuous decrease from 11.52% at 5 hr to 0.0% at 24 hr.

electron. The specific absorbed fractions for 40 keV and 70 keV were developed by interpolating the tables in Reference *2*. The specific absorbed fractions listed for 100 keV photons were used for the 103 keV photons of ^{153}Sm.

The MIRD Monte Carlo calculations are only for photons. For electrons emitted from ^{153}Sm, the Φ_{ijk} were calculated separately and along with electron Δ_i values from Reference *4*, included in Eq. (4). In general, for large source organs, it was assumed the emitted electrons were absorbed in the source organ. The exceptions include electrons emitted from the contents of the stomach, the intestines and the bladder. In these instances, electrons emitted from the source (organ contents) can reach the organ wall, and contributes to the radiation dose to the wall. The radiation dose to the wall from electrons emitted from the organ contents in each instance was assumed to be half of the internal electron radiation dose of the contents far away from the wall (*5*).

For electrons emitted from ^{153}Sm in large source organs, the specific absorbed fractions are:

$$\Phi_{ijk} = 1/M(k) \quad \text{when} \quad j = k, \qquad (5)$$
$$\Phi_{ijk} = 0.0 \quad \text{when} \quad j \neq k,$$

M(k) is the mass of source organ k.

For electrons emitted from Sm-153 in contents of bladder, stomach, and large and small intestines:

$$\Phi_{ijk} = 0.5/M(k), \qquad (6)$$

where k corresponds to the contents of organ j.

Using values of Δ_i from Reference *4* and Φ_{ijk}, described above, the "S" factors for nine source organs and 14 target organs were calculated using Eq. (4), and are listed in Table 4.

Another exception where electrons penetrate a target organ differently from the source organ are the electrons emitted from bone into red marrow. Due to the close proximity of marrow to bone, it has been demonstrated that a significant marrow radiation dose can result from electrons emitted from the bone (*6*). The dose delivered to the red marrow depends directly on the distribution of activity within the bone tissues. Generally two different types of distribution have been applied for calculating electron radiation doses from bone tissue to red bone marrow from activity within the bone structures (*6,7*). The activity is either on the bone surfaces or distributed uniformly throughout all of the bone tissues. We do not know with certainty which of these bone distributional patterns

TABLE 2
Cumulative Activities [^{153}Sm]EDTMP A
(μCi hr/mCi injected)

Organ	A (μCi-hr/mCi)
Bladder	3,056.4
Skeleton (bone)	38,448.7
Stomach	44.97
Small intestine	79.69
Upper large intestine	91.2
Lower large intestine	56.7
Kidneys	186.6
Liver	276.6
Muscle	124.9
Blood	32.03

TABLE 3
Significant ^{153}Sm Photon Emissions

Photon type	Energy (keV)	Intensity (%)	Δ(g-rad/μCi-hr)
X-ray L	5.85	11.9	0.0015*
X-ray Kα_2	40.90	17.3	0.0151*
X-ray Kα_1	41.54	31.3	0.0277*
X-ray Kβ	47	12.2	0.0123*
Gamma-ray	69.67	5.2	0.0078*
Gamma-ray	103.17	28.3	0.0622*

* These photon energies and Δ_i's were used to estimate the dose from the ^{153}Sm photons.
NCRP Report No. 58, April 1984.

TABLE 4
S, Absorbed Dose per Unit Cumulated Activity (rads/μCi-hr); ^{153}Sm

Target organs	Source Organs: Bladder contents	Stomach contents	Small intestine contents	Upper large intestine contents	Lower large intestine contents	Kidneys	Liver	Muscle	Total body
Bladder	1.49E-3	2.88E-8	1.16E-6	9.27E-7	3.15E-6	7.88E-8	4.71E-8	1.01E-6	105E-6
Skeleton (bone)	4.36E-7	5.23E-7	7.77E-7	7.03E-7	1.25E-6	9.58E-7	7.33E-7	4.46E-7	1.63E-6
Stomach	8.41E-8	1.20E-3	1.91E-6	2.24E-6	8.50E-7	1.69E-6	8.61E-7	7.46E-7	9.68E-7
Small intestine	1.34E-6	1.23E-6	7.31E-4	1.17E-5	6.28E-6	1.32E-6	7.00E-7	8.31E-7	1.18E-6
Upper large intestine	8.76E-7	1.97E-6	1.78E-5	1.33E-3	2.61E-6	1.29E-6	1.28E-6	8.76E-7	1.17E-6
Lower large intestine	4.27E-6	4.94E-7	4.96E-6	1.83E-6	2.13E-3	2.39E-7	6.87E-8	9.10E-7	1.12E-6
Kidneys	7.89E-8	1.64E-6	1.45E-6	1.31E-6	3.12E-7	2.07E-3	2.09E-6	7.96E-7	9.48E-7
Liver	4.56E-8	9.03E-7	8.42E-7	1.24E-6	7.39E-8	2.05E-6	3.35E-4	5.88E-7	1.03E-6
Muscle	1.01E-6	7.93E-7	8.31E-7	8.03E-7	9.10E-7	7.96E-7	5.88E-7	2.13E-5	8.03E-7
Marrow (red)	1.16E-6	8.41E-7	2.77E-6	2.46E-6	4.44E-6	2.54E-6	9.23E-7	1.51E-6	1.06E-4
Ovaries	3.76E-6	2.23E-7	6.59E-6	6.80E-6	1.23E-5	4.03E-7	1.60E-7	1.15E-6	1.06E-6
Spleen	2.59E-7	5.94E-6	6.27E-7	6.19E-7	3.29E-7	5.71E-6	3.49E-7	8.63E-7	1.02E-6
Testes	2.54E-6	2.00E-8	8.89E-8	7.86E-8	8.08E-7	1.97E-8	1.35E-8	6.14E-7	7.29E-7
Total body	1.16E-6	1.12E-6	1.23E-6	1.21E-6	1.22E-6	1.05E-6	1.09E-6	8.03E-7	9.29E-7

occur in humans with [^{153}Sm]EDTMP, and therefore both surface and uniform bone activity distributions were used to calculate the bone tissue and bone marrow doses.

Bone surface distribution is the more likely pattern during the first few hours following injection. The electron portions of "S" factors for bone surface cells, and its dose to red marrow used the methods described in ICRP Publication 30 (*7*) for beta emitters distributed on bone surfaces. This model includes a 120-g bone surface as a target organ, and lists absorbed fractions for bone surfaces and red marrow. The "S" factors for ^{153}Sm in surface bone using this model are shown in Table 5.

For beta activity uniformly distributed throughout bone tissue the data calculated by MIRD (*5*) for strontium-90 (^{90}Sr) was used for the electron portion of "S" factors involving ^{153}Sm bone activity. These calculations included the irradiation of marrow by electrons emitted from activity in the bone tissue. The average beta emission energy of (^{90}Sr) differs only slightly from the beta emissions of ^{153}Sm. The MIRD "S" factor data for ^{90}Sr electrons in bone and its radiation dose to bone and red marrow can be used for the ^{153}Sm electron emissions by adjusting the difference in total mean beta energy emitted from ^{90}Sr and ^{153}Sm per unit cumulated activity. The resulting "S" factors for uniform ^{153}Sm bone activity distribution are listed in Table 6.

TABLE 5
S, Absorbed Dose per Unit Cumulated Activity (rad/μCi-hr); ^{153}Sm Bone Activity Localized to Bone Surfaces Only

Target organs	Source organs: Trabecular bone	Cortical bone
Bladder	1.95E-7	1.95E-7
Skeleton (trabecular)	5.82E-4	4.50E-6
Skeleton (cortical)	4.50E-6	5.03E-4
Stomach	2.22E-7	2.22E-7
Upper large intestine	2.88E-7	2.88E-7
Lower large intestine	4.87E-7	4.87E-7
Kidneys	3.51E-7	3.51E-7
Liver	2.89E-7	2.89E-7
Muscle	4.47E-7	4.47E-7
Marrow (red)	1.94E-4	4.07E-6
Ovaries	3.92E-7	3.92E-7
Spleen	2.79E-7	2.79E-7
Testes	2.48E-7	2.48E-7
Total body	1.03E-6	1.03E-6

TABLE 6
S, Absorbed Dose per Unit Cumulated Activity (rad/μCi-hr); ^{153}Sm Bone Activity Uniformly Distributed in Bone Tissues

Target organs	Source organs: Trabecular bone	Cortical bone
Bladder	1.95E-7	1.95E-7
Skeleton (trabecular)	1.19E-4	4.50E-6
Skeleton (cortical)	4.50E-6	7.96E-5
Stomach	2.22E-7	2.22E-7
Upper large intestine	2.88E-7	2.88E-7
Lower large intestine	4.87E-7	4.87E-7
Kidneys	3.51E-7	3.51E-7
Liver	2.89E-7	2.89E-7
Muscle	4.47E-7	4.47E-7
Marrow (red)	1.37E-4	5.85E-6
Ovaries	3.92E-7	3.92E-7
Spleen	2.79E-7	2.79E-7
Testes	2.48E-7	2.48E-7
Total body	1.03E-6	1.03E-6

Calculation of Radiation Doses

The basic MIRD equation for the total radiation dose D(j) to a target organ (index j) is the sum of radiations received from the source organs (index k):

$$D(j) = \sum_k \tilde{A}(k)S(j, k). \quad (7)$$

The cumulated activities A(k) and "S" factors S(j, k) for [^{153}Sm]EDTMP were calculated as described above (see

Tables 2, 4, 5, and 6). The computer programs used to compute the $\tilde{A}(k)$ and S(j, k) arrays stored them as files that could be used to calculate the target organ doses with Eq. (7). The results of these target organ dose calculations are shown in Table 7.

DISCUSSION

The calculations presented utilized animal distribution data and the MIRD formulations for radiation dose calculation. Rapid blood clearance (blood levels of 2% at 1 hr, 0.03% at 2 hr in rats) and relatively limited photon emissions result in low doses for whole body and organs which do not significantly accumulate the [^{153}Sm]EDTMP chelate. The electron emissions from ^{153}Sm are abundant and include energies as high as 810 keV, which leads to significant radiation doses to the mucosa and walls of the GI tract and bladder, and the bone marrow. Current MIRD literature does not include values for ^{153}Sm, and we therefore derived its set of absorbed dose per unit cumulative activity ("S" factors) from MIRD tables giving specific absorbed fractions as a function of photon energy in a model of the adult human body.

The location of active marrow in the matrix of trabecular bone tissue leads to a significant "cross-over" radiation dose to the marrow from electrons emitted from ^{153}Sm deposited in the bone tissue. No theoretical or experimental microdosimetry data on ^{153}Sm for bone and bone marrow is currently available. Lacking ^{153}Sm microdosimetry, our approach using ICRP 30 data (*7*) and modified published ^{90}Sr "S" factors to estimate the bone marrow "cross-over" of ^{153}Sm emitted electrons provides a reasonably accurate description of this effect. The distribution and physical half-life of the radioactivity appears only in the cumulated activity term for the MIRD dose calculation technique, and the various cumulated activity terms were separately derived from animal data and decay properties of ^{153}Sm.

The estimated radiation doses presented provide a reasonable basis for human studies. The set of "S" factors generated for the calculations does not depend on the animal data, and can be used in conjunction with human [^{153}Sm]EDTMP distribution data to produce more accurate estimates of radiation doses associated with this agent. Other improvements in dosimetry will require direct and detailed microdosimetry calculations of bone and bone marrow concentrations, radiation transport, and better calculations of "S" factors. The generation of better "S" factors will require extensive computer simulations. Microdosimetry of trabecular bone and marrow is difficult because of nonuniformities in radionuclide deposition and variations in bone tissue and marrow geometry for distances involving electron transport.

TABLE 7
Estimated Organ Dose in rad per mCi Injected of [^{153}Sm] EDTMP (bone activity localized on surfaces only)*

Target organ	Absorbed dose per injected activity	
	rad/mCi	mGy/MBq
Bladder	4.55	1.23
Skeleton (trabecular)	11.28 (1.61)	3.05 (0.44)
Skeleton (cortical)	10.51 (2.38)	2.84 (0.64)
Stomach	0.064	0.017
Small intestine	0.078	0.021
Upper large intestine	0.138	0.037
Lower large intestine	0.153	0.041
Kidneys	0.400	0.108
Liver	0.104	0.028
Muscle	0.023	0.006
Red marrow	3.82 (2.75)	1.03 (0.74)
Ovaries	0.029	0.008
Spleen	0.013	0.003
Testes	0.017	0.004
Whole body	0.044	0.01

* Uniform bone activity distribution doses shown in parenthesis if different from model with activity on bone surfaces.

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